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Frequent Association of 22q11.2 Deletion With Tetralogy of Fallot

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Chromosome 22q11.2 deletion causes DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome with tetralogy of Fallot (TOF), and sporadic or familial TOF. To determine the prevalence and clinical importance of the 22q 11.2 deletion in TOF, a series of 212 Japanese TOF patients was studied. The type of pulmonary blood supply, which may lead to various clinical outcomes, and other additional anomalies were evaluated clinically. The 22q11.2 deletion was diagnosed by fluorescence in situ hybridization with N25 and TUPLE1 probes. Of the 212 patients examined, 28 (13%) had a 22q11.2 deletion, the frequency being higher than that in TOF patients with trisomy 21. The prevalence of the deletion in TOF patients with pulmonary atresia (PA) plus major aortico-pulmonary collateral arteries (MAPCA) was significantly higher than the value in patients with PA plus patent ductus arteriosus (PDA) ($P = 0.04$) or with pulmonary stenosis (PS) ($P < 0.0001$). All 28 patients with 22q11.2 deletion had one or more extracardiac abnormalities. Four of 9 patients with the 22q11.2 deletion and TOF-PA-MAPCA suffered from bronchomalacia, while none of 19 patients with TOF-PA-PDA or TOF-PS manifested bronchomalacia ($P = 0.006$). These results indicate that 22q11.2 deletion is the most frequent cause of syndromic TOF, especially for TOF-PA-MAPCA, and bronchomalacia is the clinically most important associated anomaly in TOF-PA-MAPCA patients. Am. J. Med. Genet. 92:269–272, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: chromosome; 22q11.2 deletion; tetralogy of Fallot; major aortico-pulmonary collateral arteries; bronchomalacia

INTRODUCTION

Chromosome 22q11.2 deletion causes DiGeorge syndrome, velocardiofacial syndrome (VCFS), and conotruncal anomaly face syndrome (CAFS) [Burn et al., 1993; Driscoll et al., 1992; Scambler et al., 1992; Wilson et al., 1993]. It results in a wide clinical spectrum, ranging from neonatal death to developmental or psychiatric problems in later life [Ryan et al., 1997]. Congenital heart defects (CHD) are among the major findings of these syndromes and mainly consist of cardiac outflow tract defects, such as tetralogy of Fallot (TOF) [Emanuel et al., 1999]. TOF is the most common cyanotic CHD, occurring in approximately 10% of infants with CHD. The anatomic hallmark of TOF is the anterocephalad deviation of the outlet septum, resulting in ventricular septal defect, aortic override, and infundibular pulmonary obstruction. The severity of pulmonary obstruction ranges from mild pulmonary stenosis (PS) to pulmonary atresia (PA). Pulmonary blood supply in TOF with PA is mediated through a patent ductus arteriosus (PDA) in two-thirds of patients and through major aortico-pulmonary collateral arteries (MAPCA) in one-third of patients [Neches et al., 1990].

There are three clinically distinguishable types of TOF, i.e., TOF with PS; TOF with PA plus PDA; TOF with PA plus MAPCA. The 22q11.2 deletion is associated with all three types of TOF [Momma et al., 1995, 1996]. Recent studies have shown that the prevalence of 22q11.2 deletion among patients with TOF was 8–17% [Amati et al., 1995; Digilio et al., 1996; Goldmuntz et al., 1998; Johnson et al., 1996; Webber et al., 1996]. However, its prevalence in syndromic and isolated TOF remains to be studied. As our previous study of 183 patients with CAFS showed a high association between the 22q11.2 deletion and TOF with PA+MAPCA [Matsuoka et al., 1998], we speculated that the prevalence may differ among the three TOF types. The purpose of this study was to know the preva-

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lence of 22q11.2 deletion in a large number of patients with different types of TOF.

PATIENTS AND METHODS

The subjects studied included 212 (125 males and 87 females) consecutive Japanese patients with TOF who visited our hospital from June 1994 to June 1999. Their ages ranged from 15 days to 34 years and the median age was 11 years. The patients were clinically divided into the following three types, according to clinical definitions shown in Table I: patients with TOF-PS (classical or common TOF); those with TOF-PA-PDA; and those with TOF-PA-MAPCA. Cardiac diagnosis in all the 212 patients was made by echocardiography, cardiac catheterization, and/or findings at cardiac surgery. Fluorescence in situ hybridization (FISH) was performed, as described previously [Matsuoka et al., 1998], in 196 patients who did not have trisomy 21. The probes used were N25 (*D22S75*) (Oncor, Gaithersburg, MD) and TUPLE1 (Vysis, Downers Grove, IL). The patients were examined as to whether they had additional extracardiac anomalies. Facial features characteristic of the 22q11.2 deletion syndrome were judged by one geneticist and by two cardiologists independently. By these careful examinations, TOF patients without other anomalies and normal karyotypes were classified as having isolated TOF, while those with one or more other anomalies and/or chromosomal abnormalities were grouped as having syndromic TOF. Fisher's exact probability test was used for group comparisons, and $P < 0.05$ was defined as significant.

RESULTS

Of the 212 patients examined, 173 (82%) had TOF-PS, 22 (10%) TOF-PA-PDA, and 17 (8%) had TOF-PA-MAPCA. FISH analysis demonstrated a 22q11.2 deletion in 15 (9%) of the 173 TOF-PS cases, 4 (18%) of 22 TOF-PA-PDA cases, and in 9 (53%) of 17 TOF-PA-MAPCA cases (Table II, Fig. 1). Thus, the prevalence of the 22q11.2 deletion was significantly higher in patients with TOF-PA-MAPCA than that in patients with TOF-PA-PDA ($P = 0.04$) or with TOF-PS ($P < 0.0001$). However, there was no significant difference ($P = 0.24$) in prevalence between TOF-PS and TOF-PA-PDA patients. The overall prevalence of 22q11.2 deletion in TOF patients was estimated at 13% (28/212 cases).

TABLE II. Prevalence of 22q11.2 Deletion in Tetralogy of Fallot (TOF) Patients*

Cardiac diagnosis[A]	Number of patients	Number of cases of deletion (%)
TOF-PS	173	15 (8.6)
TOF-PA-PDA	22	4 (18.2)
TOF-PA-MAPCA	17	9 (5.3)
Total	212	28 (13.2)

*TOF-PS = Tetralogy of fallot with pulmonary stenosis; PA = pulmonary atresia; PDA = patent ductus arteriosus; MAPCA = major aortico-pulmonary collateral arteries.

According to the clinical manifestations and karyotypes observed, the 212 patients were classified into two groups: 146 (69%) patients with isolated TOF and 66 (31%) patients with syndromic TOF (Table III). The patients with syndromic TOF included 28 (13%) cases of the 22q11.2 deletion syndrome, 16 (7.5%) with Down syndrome, and one each with Ulrich-Turner syndrome, trisomy X, partial monosomy for 10q, Goldenhar syndrome, Brachmann-de Lange syndrome, and Cantrell sequence. Three patients had facial anomalies similar to the 22q11.2 deletion syndrome but had no deletion. The remaining 13 patients had extracardiac anomalies (Table III). All these 28 patients with the 22q11.2 deletion had facial anomalies characteristic of the 22q11.2 deletion syndrome (Fig. 2), whereas no patients without characteristic face had the deletion.

As frequencies of the 22q11.2 deletion were quite different between patients with TOF-PA-MAPCA and those with the two other types of TOF, we analyzed whether the difference was associated with other extracardiac anomalies. Among several anomalies, bron-

TABLE I. Clinical Definitions of Tetralogy of Fallot (TOF) by Cardiac Anatomy and Other Associated Abnormalities

Cardiac anatomy	
TOF-PS	Tetralogy of Fallot with pulmonary blood flow through stenotic pulmonary outflow tract
TOF-PA-PDA	Tetralogy of Fallot with pulmonary atresia and pulmonary blood flow through ductus arteriosus
TOF-PA-MAPCA	Tetralogy of Fallot with pulmonary atresia and pulmonary blood flow through collateral arteries originating from the descending and ascending aorta
Associated abnormality	
Aortic arch abnormality	Right aortic arch, elongation of aorta, aberrant subclavian arteries
Characteristic facial feature	Ocular hypertelorism, narrow palpebral fissures, bloated eyelids, low nasal bridge, small mouth, deformed earlobe
Otolaryngeal abnormality	Cleft palate (hard/soft/submucous), velopharyngeal insufficiency
Hypoparathyroidism	Transient decreasing serum calcium below 7.0 mg/dL episode of tetany or convulsion due to hypocalcemia
Mild mental retardation	Intelligence quality or developmental quality below 85
Bronchomalacia	Recurrent episodes of respiratory distress and collapse of bronchus by 75% or more during exhalation examined by bronchofiberscopy

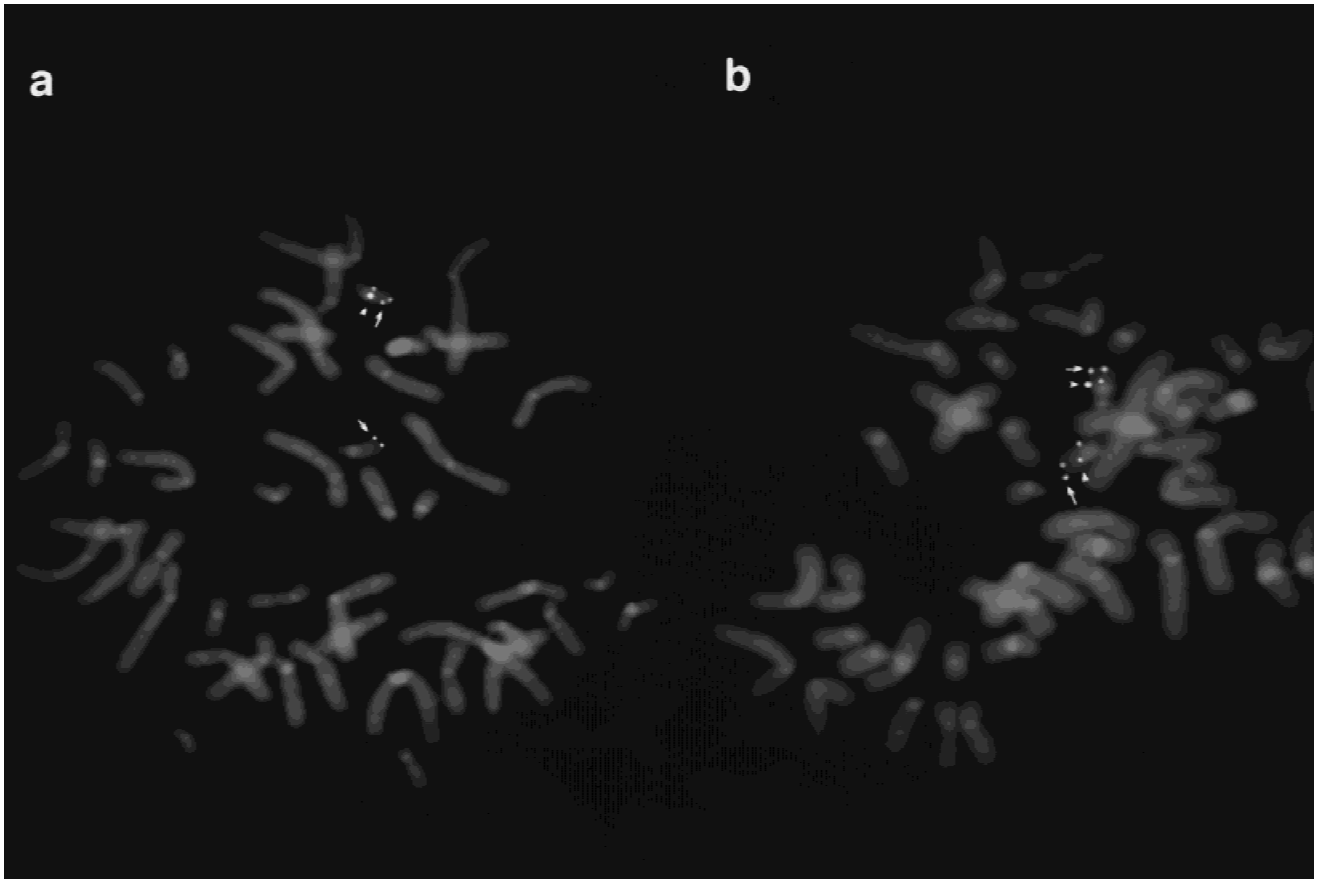

Fig. 1. Fluorescence in situ hybridization with N25 probe. Control signals for 22q13.3 probe (arrows) show two chromosome 22s, both in a patient with 22q11.2 deletion **(a)** and a normal individual **(b)**. Signal for N25 (arrowheads) appear on only one of the chromosome 22s in the patient (a), whereas on two chromosome 22s in the normal individual (b).

chomalacia was highly associated with TOF-PA-MAPCA ($P < 0.006$) (Table IV).

DISCUSSION

In the present series of TOF patients, the prevalence of the 22q11.2 deletion was calculated to be 13%. The value obtained is very comparable with that in previous studies in western countries [Amati et al., 1995; Digilio et al., 1996; Goldmuntz et al., 1998; Johnson et al., 1996; Webber et al., 1996], suggesting no significant racial difference in the prevalence. The estimated overall prevalence of the deletion was about 1.8 times higher than that of trisomy 21. As we first speculated, the prevalence (53%) was significantly higher in patients with TOF-PA-MAPCA than in those with TOF-PS or TOF-PA-PDA. This value (53%) is similar to that

TABLE III. Prevalence of 22q11.2 Deletion and Other Syndromes in 212 Patients With Tetralogy of Fallot (TOF)

Clinical and cytogenetic diagnosis	Number of patients (%)
Isolated TOF	146 (69)
Syndromic TOF	66 (31)
22q11.2 deletion syndrome	28 (13)
Down syndrome	16 (7.5)
Ulrich-Turner syndrome	1 (0.5)
Trisomy X	1 (0.5)
Partial monosomy for 10q	1 (0.5)
Goldenhar syndrome	1 (0.5)
Brachmann-de Lange syndrome	1 (0.5)
Cantrell sequence	1 (0.5)
TOF with extracardiac abnormalities (no definitive diagnosis)	16 (7.5)
Total	212 (100)

Fig. 2. Facial appearance of the patient.

TABLE IV. Associated Abnormalities in 28 Patients With 22q11.2 Deletion and Different Tetralogy of Fallot (TOF) Types

	TOF-PS and TOF-PA-PDA[a] (n = 19)	TOF-PA-MAPCA[b] (n = 9)
Aortic arch anomalies	7 (37%)	5 (56%)
Characteristic facial anomalies	19 (100%)	9 (100%)
Otolaryngeal abnormalities	6 (32%)	3 (33%)
Hypoparathyroidism	4 (21%)	2 (22%)
Renal abnormalities	2 (11%)	1 (11%)
Anal atresia	1 (5%)	1 (11%)
Mild mental retardation	8 (42%)	7 (78%)
Bronchomalacia	0 (0%)	4 (44%)[c]

[a]PS = pulmonary stenosis; PA = pulmonary atresia; PDA = patent ductus arteriosus.
[b]MAPCA = major aortico-pulmonary collateral arteries
[c]Frequency, significantly different (p = 0.006).

in patients with interruption of aortic arch type B, which has been known as the most commonly associated CHD with 22q11.2 deletion [Goldmuntz et al., 1998; Lewin et al., 1997]. These results indicate that 22q11.2 deletion is the most frequent genetic cause for syndromic TOF, especially for TOF-PA-MAPCA.

All patients with the 22q11.2 deletion examined had characteristic facial anomalies, and most had one or more additional extracardiac abnormalities, whereas no patients with normal face had either the 22q11.2 deletion or such additional anomalies. We, thus, conclude that most isolated TOF may not be associated with the 22q11.2 deletion. It is likely that previously reported patients with both isolated TOF and the 22q11.2 deletion [Goldmuntz et al., 1993; Goldmuntz and Emanuel, 1997] had some subtle extracardiac abnormalities, as observed in our patients.

Our study also showed that bronchomalacia was highly associated with TOF-PA-MAPCA but not with TOF-PS or TOF-PA-PDA. In contrast, most other extracardiac abnormalities were similarly seen in both groups. Association of bronchomalacia with the 22q11.2 deletion has not previously been described. Jedele et al. [1992] described significant bronchospasm in 7 of 15 patients with VCFS and TOF-PA-MAPCA. Our patients with bronchomalacia manifested episodic respiratory distress reminiscent of bronchospasm, and all of them required pre- and postoperative critical respiratory care and have not been able to get complete surgical repair. One of them suddenly died of severe respiratory distress at age 2 years. Thus, the association of bronchomalacia needs to be considered in patients with the 22q11.2 deletion and TOF-PA-MAPCA, because it may lead to major life-threatening complications. It remains to be clarified why bronchomalacia is associated with the 22q11.2 deletion in TOF-PA-MAPCA patients.

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